Vitamin D Resistant Rickets

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• **Vitamin D resistant rickets is not a rare disorder. Increased awareness of this metabolic disorder during the examination of children with bowed legs, even infants receiving normal supplements of vitamin D, may lead to diagnosis oftener. Ten previously unrecorded cases of this disorder are included within this report. Three of the patients had associated congenital anomalies which also required treatment. Treatment of the vitamin D resistant rickets consists of the oral administration of large doses of vitamin D. Careful observation of patients during vitamin D therapy to prevent overdosage and resultant hypercalcemia is of utmost importance.**

Surgical correction of the bony deformities is rarely necessary.

The cause of vitamin D resistant rickets is thought to be a defect of renal tubular mechanisms.

THE SYNDROME of rickets resistant to normal therapeutic doses of vitamin D but amenable to massive doses was first described by Albright, Butler and Bloomberg in 1927.[1,2] Until 1950, the number of known cases was approximately 30,[11] but increased awareness of this entity has brought the total of reported cases to over 75.[13,18,21,24,25] The authors' experience with ten cases will be reviewed with emphasis on the clinical features, pathogenesis, differential diagnosis, treatment and associated congenital anomalies (Chart 1).

REPORTS OF CASES

CASE 1. The patient was noted by her parents to have "peculiar legs" from birth. Bowing of the legs became increasingly evident when she began to walk, in spite of persistent orthopedic measures. At the age of three and a half years, she was sent to the U.C.L.A. Pediatric Clinic with a tentative diagnosis of rickets resistant to vitamin D. Dietary history was normal, including 1,000 to 2,000 units of vitamin D in a water-miscible vehicle daily since birth. Upon physical examination, moderate bowing of all leg bones, and moderate enlargement of the costochondral junctions and wrists were noted. In addition, the shape of the skull was quite unusual; although the circumference was normal, the head appeared narrow and elongated. Examination of the ocular fundi by an ophthalmologist confirmed the presence of papilledema. Both eyes appeared unduly prominent. Roentgen studies of the long bones showed bowing, hypomineralization and cupping, fraying and spreading of metaphyses. Numerous views of the skull provided radiological evidence of premature closure of the sagittal cranial suture (or overmineralization). The blood calcium was within the normal range, the phosphorus content 2.6 mg. per 100 cc., and alkaline phosphatase slightly above the normal range. No abnormalities of fat absorption, acidosis or gross renal function could be demonstrated. Amino-aciduria was demonstrated by paper chromatography. Excretion of beta amino isobutyric acid, methyl histidine, glycine and serine was especially high.

A diagnosis of vitamin D resistant rickets and premature closure of the cranial sutures was made. Surgical treatment of the skull resulted in relief of papilledema. Vitamin D administration in dosages ranging from 50,000 to 150,000 units a day resulted in pronounced improvement in the rachitic lesions, as well as decreased amino-aciduria.

CASE 2. A girl was referred to the U.C.L.A. Pediatric Clinic at two years of age for evaluation of bowed legs. She had received normal amounts of vitamin D since she was two weeks of age. X-ray studies of the lower extremities showed changes typical of rickets. Results of urinalysis were normal. The blood calcium level was 10.6 mg. per 100 cc., phosphorus 3.0 mg. per 100 cc., and alkaline phosphatase 35 King-Armstrong units. Blood urea nitrogen, bicarbonate content and chloride content were within normal limits. Intravenous pyelography was carried out and no abnormalities were seen. Urinary chromatographic studies showed elevated excretion of amino acid. Therapy with 75,000 units of vitamin D daily resulted in return of the amino acid excretion to normal and in cure of the disease as determined clinically and roentgenographically. However, the serum phosphorus level continued below the lowest level of the normal range. Attempts to correct this chemical abnormality by giving buffered sodium phosphate and citrate by mouth were unsuccessful. At the time of last report maintenance therapy consisted of 45,000 units of vitamin D daily.

CASE 3. The patient, a girl, was seen by one of the authors at four years of age after one and one-half years of unsuccessful orthopedic measures for correction of bowed legs. She had received normal doses of vitamin D since infancy. Upon x-ray study,

Presented before the Section on Pediatrics at the 85th Annual Session of the California Medical Association, Los Angeles, April 29 to May 2, 1956.

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Clinical and Laboratory Data in Ten Cases of Vitamin D Resistant Rickets

Case No.	Age Yr.	Age Mo.	Familial Incidence	X-ray Evidence of Rickets	Serum Calcium	Serum Phosphorus	Serum Alk. Phosphatase	Associated Anomalies	Response to Therapy with Vitamin D
1.	3	6	None	Positive	Normal	Low	Elevated	Synostosis cranei	Clinical cure
2.	2		None	Positive	Normal	Low	Elevated	None	Decided improvement
3.	4		Unknown	Positive	Normal	Low	Elevated	None	Decided improvement
4.	1	9	None	Positive	Normal	Low	Elevated	Sparse hair; congenital amputation of wrist; defective dentition	No response
5.	2	11	None	Positive	Normal	Low	Elevated	Chronic acidosis due to renal tubular defect	Untreated as yet
6.	3	9	None	Positive	Normal	Low	Elevated	None	Decided improvement
7.	3	6	3 members	Positive	Normal	Low	Elevated	None	Clinical cure; plus osteotomy
8.	1	7	3 members	Equivocal	Normal	Slightly decreased	Elevated	None	Untreated as yet
9.	3	10	3 members	Positive	Normal	Low	Elevated	None	Decided improvement
10.	2	6	3 members	Positive	Normal	Low	Elevated	None	Decided improvement

the condition of the lower extremities and wrists was observed to be typical of rickets. Blood phosphorus was 3.0 mg. per 100 cc., the alkaline phosphatase value 18 Bodansky units and the calcium content 10.0 mg. per 100 cc. Results of electrolyte studies of the blood were otherwise normal. Results of urinalysis were within normal limits. Vitamin D, 50,000 units daily, was given and the patient showed steady clinical and roentgenological improvement.

CASE 4. A 6-year-old girl, was first seen at the U.C.L.A. Pediatric Clinic with a resistant case of rickets that had been diagnosed when the patient was 21 months of age. Treatment in the past included the daily administration of up to 2,000,000 units of vitamin D. Parenteral administration of large doses of vitamin D was also attempted. According to the mother, no vitamin D had been administered during the three years preceding the child's admission to the clinic. Upon physical examination, pronounced anterior bowing of both lower legs, cranial bossing, lumbar lordosis and congenital amputation of the right forearm at the wrist were noted. Multiple ectodermal defects were present. There were several xanthomata on the legs. The hair was extremely sparse, and only four deciduous teeth remained. The child perspired very freely at normal environmental temperatures.

The amounts of electrolytes in the blood were within normal limits, with the exception of serum phosphorus, which was below the normal range. The serum alkaline phosphatase activity was 23 King-Armstrong units. Cystine crystals were not found in the bone marrow aspirate. High levels of phosphorus were repeatedly demonstrated in the urine during periods of normal and low intake of phosphorus. During the administration of calcium intravenously, the urinary content of phosphorus decreased, indicating a normal parathyroid response. During the period when no vitamin D therapy was given, rachitic bone changes, visible by x-ray examination, improved noticeably. Although most of the usual diagnostic criteria of vitamin D resistant rickets were present in this case, the possibility of hypersensitivity to vitamin D was being considered at the time of this report.

CASE 5. A 3-year-old girl was admitted to the U.C.L.A. Hospital because of roentgenographic observations and results of chemical analysis of the blood consistent with resistant rickets. Since infancy the patient had been given vitamins sufficient for normal needs. Although her appetite was poor, she ingested large amounts of orange juice. There was no familial history of rickets.

The child appeared to be alert. Moderate retardation of linear growth and lateral bowing of the lower legs were noted. The blood phosphorus was 3.8 mg. per 100 cc., calcium content 10.6 mg. per 100 cc. and alkaline phosphatase 23 King-Armstrong units. Blood electrolyte studies showed a reduced bicarbonate content on several occasions and on two occasions an elevated serum chloride content. The urine showed a reduced titrable acidity and decreased ammonia production. With rare exception, the pH of the urine remained more alkaline than pH 7.0 in spite of compensated systemic acidosis. These findings suggested that hyperchloremic renal acidosis of mild degree was the cause of the rachitic changes. In addition to increased dosage of vitamin D, oral administration of alkaline salt mixture resulted in improvement of the rickets.

CASE 6. The patient, a girl three and a half years of age, had progressive bowing of the legs since starting to walk. X-rays showed profound osteo-

malasia with other typical rachitic changes. The blood phosphorus level was 3.0 mg. per 100 cc., blood calcium 10.1 mg. per 100 cc. and alkaline phosphatase 13.9 Bodansky units. During administration of 150,000 units of vitamin D daily, toxic symptoms of nausea, vomiting and hematuria developed. Reduction of the dose to 100,000 units brought prompt relief of symptoms. Clinical response of the rickets resulted from this therapy over a period of two months. When last seen, the patient was again taking 150,000 units daily with continued improvement.

CASE 7. A 3-year-old boy, was admitted to Shriners' Hospital with complaint of bowed legs noted since he was 14 months of age. Vitamin D sufficient for normal needs had been given since infancy. In addition to typical roentgenologic features of rickets, there was a decreased blood phosphorus level (3.3 mg. per 100 cc.), elevated alkaline phosphatase (32.4 King-Armstrong units), and normal blood calcium (9.7 mg. per 100 cc.). Up to 150,000 units of vitamin D was given for six months. Bilateral femoral osteotomy was then done. Thereafter the patient was given 75,000 units of vitamin D daily and was clinically well. (The patient's mother had bilateral osteotomy for bowed legs at the age of 14 years. She had never received additional vitamin D therapy. She is now 4 feet 9 inches tall and it is assumed that she also had resistant rickets.)

CASE 8. The patient, a sister of the patient in Case 7, 2 years of age, was examined because of the familial history. No clinical symptoms of rickets were observed. X-ray films of the lower extremities, however, showed minimal rachitic changes. The blood calcium was 10.3 mg. per 100 cc., phosphorus 3.7 mg. per 100 cc. and alkaline phosphatase 24.0 King-Armstrong units.

CASE 9. A 4-year-old girl had a history of increased lateral bowing of the legs, observed over a period of a year. Her mother had had rickets and, at the age of six years, had had bilateral osteotomy for repair of the bowing. The mother was 4 feet 7½ inches tall. Less than normal linear growth and advanced rachitic changes were observed in roentgen studies. The phosphorus content of the blood was 3.7 mg. per 100 cc., calcium 10.4 mg. per 100 cc. and alkaline phosphatase 26 King-Armstrong units. After six weeks of therapy with 100,000 units of vitamin D daily, improvement was observed roentgenographically.

CASE 10. When the sister of the patient in Case 9, 28 months of age, was examined, diminished stature was the only abnormality noted clinically. X-ray films of the long bones showed definite rachitic changes. Blood alkaline phosphatase was 45.0 King-Armstrong units, phosphorus content 3.2 mg. per 100 cc. and calcium content 9.6 mg. per 100 cc. Rachitic changes in the bones, as roentgenographically observed, were improved after six weeks of vitamin D therapy.

DISCUSSION

The usual clinical manifestations of vitamin D resistant rickets are similar to those of vitamin D deficiency rickets. Both probably begin within the first year, but whereas the latter usually is diagnosed early, rarely is resistant rickets diagnosed in a patient less than one year of age, perhaps because suspicion of rickets is not high in a patient so young who is receiving the usual daily supplement of vitamin D. Usually with both kinds of rickets the first symptom noted is bowing of the legs with concomitant shortening of stature. The bowing may be in a lateral, medial or anterior direction, lateral most often. Cranial bossing, beading of the ribs and enlargement of the knees, wrists and ankles may also be present.

In the very early stages of the disease, rickets cannot be detected roentgenographically. This is particularly true if the roentgen studies do not include the distal parts of the lower extremities at the time of evaluation of bowed legs, since the earliest changes occur at the site where the bone growth is most rapid. The first roentgenographically observable changes occur at the epiphyseal plate. Normally the plate is sharply defined, but in a patient with rickets there is a frayed appearance at the metaphyseal-epiphyseal junction which is caused by irregular osteoblastic deposition of bone salt resulting from continued, but disorderly, resorption of the cartilagenous osteoid tissue in this rapidly growing area. The most common sites of such involvement in rickets are the distal femur and the distal ends of the ulna and tibia. As the rachitic process continues, demineralization of the shaft occurs, owing to a loss of lime. As a consequence of this softening of the bone, bowing and, occasionally, fractures may occur.

Chemical studies of the blood in a typical case show decreased serum phosphorus concentration and elevated alkaline phosphatase activity. Blood calcium levels may be normal or slightly depressed.

Resistant rickets is generally considered to have a familial basis, although reports of sporadic cases are numerous.

Pathogenesis

Fanconi's concept of "phosphate diabetes" due to selective tubular deficiency as the primary mechanism in resistant rickets is in general agreement with that of most investigators. Robertson and co-workers[20] were the first to express this concept. Other observers, including Winberg and co-workers[25] who recently reported on the subject, could not demonstrate the increased tubular excretion of phosphorus in untreated resistant rickets. Perhaps certain cases may have a different pathogenesis, and perhaps not all vitamin D resistant rickets is of the same type.

However, most of the cases described herein, as well as the majority of cases reported in the literature, appear to be a variant of the Debre-de Toni-Fanconi syndrome, where some degree of tubular dysfunction is evident. In two of the cases reported herein, abnormal urinary amino acid excretion was demonstrated by paper chromatographic methods. Fishman and Jonxis also observed this condition in patients with vitamin D resistant rickets.[10,15,16] The amino-aciduria may possibly result from the same basic defect as does the phosphaturia.

Although faulty intestinal absorption of vitamin D may bring about the clinical features of rickets, this defect was not present in the patients under consideration. Normal vitamin D levels may be demonstrated in the blood of patients with vitamin D resistant rickets at a time when the patient is receiving only small doses of vitamin D by mouth, even while the disease is in its active state.[3,8]

There are two primary sites of action of vitamin D. The greatest action is in the intestine, where vitamin D increases the absorption of ingested calcium and, as a consequence, the absorption of ingested phosphorus. Vitamin D also acts on renal tubules. Its mechanism of action there is not well understood. Albright postulated that the greater tubular efficiency of phosphate reabsorption is the result of parathyroid inhibition which has resulted from the high intestinal absorption of calcium. In patients with vitamin D resistant rickets, this mechanism is further complicated. The reasons for the hyperphosphaturia and amino-aciduria are not as yet fully explained. Jonxis was unable to demonstrate abnormal amino-aciduria in patients with hyperparathyroidism, implying that parathyroid hormone is not responsible for amino-aciduria in resistant rickets.[14] Thus, even though patients with vitamin D resistant rickets are known to have increased parathyroid activity, it would appear that this is a secondary rather than a primary phenomenon. Compensatory parathyroid hyperactivity accounts only for the normal blood calcium levels usually found in this condition. From the available evidence, it would seem that the primary defect in vitamin D resistant rickets lies within the renal tubular cell and is associated with a poorly understood enzymatic process which may be dependent upon vitamin D for its action.

Differential Diagnosis

Vitamin D resistant rickets must be differentiated from conditions which may cause similar abnormality in growth of bones. Congenital abnormalities of the lower extremities, such as femoral bowing, coxa varum, coxa valgum and bony defects associated with dimpling of the overlying skin, must be considered. Other, more generalized congenital defects, such as chondrodystrophy and osteochondrodystrophy, may simulate vitamin D resistant rickets in the early forms of each. These other conditions are not associated with abnormalities in the blood concentrations of calcium, phosphorus and alkaline phosphatase, nor do they respond to therapy with vitamin D.

Rathbun[21] recently described an inborn error of metabolism which is associated with an abnormality in the metabolism of alkaline phosphatase.[21] This condition may simulate vitamin D resistant rickets in clinical and radiological characteristics. Differential diagnosis from resistant rickets is made on the basis of chemical studies of the blood. In this condition, which has been called "hypophosphatasia," the blood calcium levels are normal or high, the serum phosphorus levels are normal, and the alkaline phosphatase activity of the serum is depressed or absent. Vitamin D in large doses does not improve the condition.

Lead poisoning in its chronic form has, at times, been associated with amino-aciduria, hypophosphatemia and rachitic changes in the bones.[6] The chemical contents of the blood may also be abnormal. These rachitic changes are the result of an excessive loss of calcium in the stool as calcium soaps. In addition, there is a failure of intestinal absorption of the fat-soluble vitamin D. Steatorrhea, therefore, may result in rickets which does not respond to oily solutions of vitamin D administered orally.

When it has been established that the problem is truly that of rickets which does not respond to the usual low dosage level which will cure vitamin D deficiency rickets, one must consider whether additional metabolic defects are present. Renal acidosis, as seen in the classical Fanconi syndrome, and the hyperchloremic syndrome described by Albright must be considered. Therapy with large doses of vitamin D alone in these conditions is not sufficient.

Treatment

Satisfactory clinical healing of the rachitic lesions in patients with uncomplicated vitamin D resistant rickets usually results when from 50,000 to 150,000 units of vitamin D is given daily. Occasionally a patient will require considerably larger doses before a response can be noted. The vitamin D should be administered by mouth, since there is no defect in the absorption by this route.

The earliest response to proper treatment can be best evaluated by x-ray films of the bones. This is manifest by finding a linear increase in density in the rachitic metaphysis at the rapidly growing ends of the long bones, which results from an increased and more orderly deposition of bone salt in this area and eventually progresses to a broad, dense, transverse line. As healing continues, x-ray films

will show a disappearance of the cupping, as well as a decreased distance between the calcified portions of the metaphyses and epiphyses. Later, the density of the shafts of the long bones increases. Gradual disappearance of the bowing and other bony deformities accompanies this process. Whether the deformity will be completely overcome depends upon the severity of involvement at the beginning of therapy, the age at which therapy is begun, and the adequacy of therapy on an individual basis.

In addition to radiological observation of progress, chemical evidence may be obtained of the effect of large doses of vitamin D. The earliest of these is a return of the elevated alkaline phosphatase activity of the serum to normal levels. This evidence may not be present as early as radiologic evidence of healing. In resistant rickets, unlike ordinary rickets, the return of the serum phosphorus level to normal occurs late. In some patients this may not occur until several years after therapy is begun.[11,22] (Attempts to accelerate the return of inorganic phosphorus level to normal in one of the patients treated by the authors, by increasing the dietary intake of phosphorus, were unsuccessful.)

Theoretically, the administration of citric acid and citrate should be of some benefit. This organic acid combines with bone salt as an integral part of the crystalline framework of bones. The citric acid content of bone may be experimentally increased by the administration of vitamin D. The citric acid content of the blood rises during the administration of vitamin D, as well as with calcium administration alone. Increasing the amount of phosphorus in the diet appears to have no effect on blood citric acid levels.[5] Harrison[12] demonstrated that the level of citric acid in the blood in children with vitamin D deficiency rickets averages only 1.5 mg. per 100 cc., as compared with the normal of 2.5 mg. The administration of vitamin D caused this level to return to normal. In rats, diets low in calcium and phosphorus will produce rickets and the administration of citric acid and sodium citrate will promote healing of rachitic lesions, even though the rat continues to receive a diet low in calcium and phosphorus.[26]

In spite of these fragments of indirect evidence which would suggest that additional citrate should be of benefit in the therapeutic regimen of patients with vitamin D resistant rickets, this has not been the case.[8] In another attempt to accelerate the return of the serum inorganic phosphorus level to normal in one of our patients, we administered large doses of citrate in addition to vitamin D. There was no detectable improvement in the serum phosphorus level.

The dangers of using large doses of vitamin D can be great, unless proper precautions are taken. Hypercalcemia with resultant soft tissue calcification and particularly renal calcification may result unless adequate control is maintained. We have arbitrarily chosen 12 mg. of calcium per 100 cc. of blood as the upper safe limit. When this level is reached, regardless of the state of healing of the rachitic process, the dosage of vitamin D must be reduced. The content of calcium in the blood of all patients receiving large daily doses of vitamin D is determined monthly. Although we have attempted to evaluate the calcium levels of these patients by use of the Sulkowitch reagent for testing the urine, this has not proved satisfactory. The correlation of results of this urine test with blood calcium determinations has been poor; in some cases hypercalcemia has developed in the face of normal results of the urine tests.

Although the dosage necessary for promoting healing early in the disease may be somewhat greater than the dosage required after healing is well under way, there appears to be no predictable formula for calculating individual dosage levels. In our experience, repeated evaluation over periods as long as a year may be required to reach the proper dosage level, since hypercalcemia may develop very slowly. A complicating situation results when a patient receiving large doses of vitamin D is suddenly immobilized. In such circumstances the blood calcium level may rise to dangerously high levels, with resultant deposition of calcium in soft tissues, particularly in renal tubules. It seems desirable to discontinue high levels of vitamin D well in advance of predictable periods of immobilization, such as for elective operation to correct orthopedic deformities. Nausea and vomiting may be due either to the toxic effects of overdosage or to the gastric irritation of the vitamin D per se.

The continuing high requirement of vitamin D is usually evident until the end of the growth period, when the epiphyses close. In the majority of children treated before the age of five years, surgical correction of the deformities is unnecessary. Surgical results are poor in patients who have had no previous vitamin D therapy, and a return of the deformities is to be expected.

Associated Abnormalities

Three of the ten children included in this report had associated congenital abnormalities. The patient in Case 1 had premature closure of the cranial sutures with resultant increased intracranial pressure. Although this anomaly is not uncommon with other forms of congenital disorders of bone metabolism, it has been reported only twice previously in association with vitamin D resistant rickets.[7,13] In Case 5 the patient had chronic acidosis associated with alkaline pH of the urine and decreased ability of the renal tubule to produce ammonia. In this

case the bone disease did not respond to vitamin D until alkali therapy was added. The patient in Case 4 had multiple ectodermal defects in addition to the apparent resistance to extremely high doses of vitamin D. A similar association of vitamin D resistant rickets and ectodermal defects was reported by Imerslund.[13] In the case here reported, radiologic improvement of the rachitic deformities occurred during a three-year period when no vitamin D was given. Spontaneous improvement of the rachitic process is very unusual in these patients. Hence it is possible that the patient in Case 4 may be hypersensitive to vitamin D rather than resistant to it. A similar case was reported by Van Creveld.[23]

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